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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,760	07/17/2003	David L. Lewis	Mirus.030.09.2	9319

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MIRUS CORPORATION
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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,760	LEWIS ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/11/2006 has been entered.

2. Claim 4 has been cancelled. Claims 6-9 have been amended.

Claims 1-3 and 5-9 are pending and under examination.

Formal matters in the Claims

3. The claim listing is objected to because the claim listing does not indicate the correct status of the claim 5. Claim 5 is indicated as "currently amended", while the correct status is "previously presented". Appropriate correction is required. Applicant is advised that Response to all matters raised in the Office Action is required, otherwise a Response may be found Non-Responsive.

Oath/Declaration

4. The Examiner acknowledges Applicant's arguments and recognizes that the oath/declaration is acceptable.

Claim Objections

5. It is noted that the amendments to the claims were sufficient to obviate the objection made in the final Office action.

Priority

6. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 10/345,021, and 10/186,757, 10/157,654 (now Patent No. 7,101,995), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The instant claims disclose a composition for delivering an siRNA to a cell and a method of delivering the siRNA to a cell by using the composition, wherein the composition comprises an amphipathic compound, polyvinylamine, and an siRNA. The instant claims are specifically directed to

polyvinylamine. However, the applications above do not provide support for the use of a composition comprising polyvinylamine and therefore, the priority date for the instant application is its filing date, i.e., 07/17/2003.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-3 and 5-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent No. 5,744,335, in view of both Wolfert et al. (Bioconjugate Chem, 1999, 10: 993-100, of record) and Leake et al. (PGPUB 2004/0224405). Although the conflicting claims are

not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to (i) a deliverable composition comprising an amphipathic compound, polyvinylamine and siRNA (claim 1); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes and R1 and R2 are the same (claims 2 and 3), and (ii) a process for delivering a siRNA to an animal cell by using the above-mentioned composition, and wherein the animal cell is *in vivo*, *in vitro*, *ex vivo* or the cell is a mammalian cell (claims 5-9). The specification discloses that the amphipathic compound may be mixed with the polyvinylamine after the addition of siRNA (i.e., siRNA encapsulation by the amphipathic compound is not required for transfection) (p. 3, paragraph 0020).

The patent claims recite a process for transfecting a polynucleotide into a mammalian cell by delivering a composition comprising and amphipathic compound, a histone as a polynucleotide-binding protein, and the polynucleotide, wherein encapsulation of the polynucleotide by the amphipathic compound is not required for transfection (claims 1 and 2), wherein the amphipahic compound is a 1,4 disubstituted piperazine and wherein the substituting groups are C6 to C24 alkenes (claims 6 and 7). The specification defines that R1 and R2 could be the same and the polynucleotide can be an antisense oligonucleotide (Summary of the invention, lines 54-67, column 7, lines 14-17). The patent claims do not recite polyvinylamine. Wolfert et al. teach that cationic polymers such as polyvinylamine efficiently condensate the nucleic acids and form small complexes with good extracellular stability (Abstract, p. 999, column 1,

Results). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of the '335 patent by replacing the histones with polyvinylamine and use it to deliver siRNAs to the nucleus, as taught by Wolfert et al., with a reasonable expectation of success. One of skill in the art would have been motivated to replace the ansisense oligonucleotide with an siRNA because siRNA are more efficient than antisense oligonucleotides in inhibiting gene expression. The motivation to use polyvinyl amine in combination with siRNAs is provided by Wolfert et al. who teach that the use of polyvinylamine results in small complexes that are stable in circulation, can undergo extravasation in the target tissues and can easily enter into the nucleus of target cells (Abstract, p. 1003, column 2, p. 1002, column 2) and by Leake et al., who teach the necessity of targeting the siRNAs to the nucleus to target non-coding nucleic acid sequences, such as promoters or enhancers (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). With respect to the limitations recited in the instant claims 6-8, they are not innovative over the prior art; one of skill in the art would have known that such compositions could be used to deliver siRNAs *ex vivo*, *in vivo*, or *in vitro*. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. Claims 1-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7,101,995, in view of both Wolfert et al. and Leake et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

** It is noted that the same rejection was made in the non-final Office action of 04/04/2006. Applicant argued that ethoxylated polyethyleneimine and polyvinylamine are patentably distinct and the rejection was withdrawn in the final Office action of 09/19/2006. However, upon further consideration, the rejection is again applied in the present Office action. It is noted that, although are distinct, the instant inventions are both directed to novel amphipathic compounds that are used to prepare novel complexes for siRNA delivery in combination with a variety of polycations, such as ethoxylated polyethyleneimine and polyvinylamine and not to ethoxylated polyethyleneimine and polyvinylamine *per se*. Since both ethoxylated polyethyleneimine and polyvinylamine were used in the art for nucleic acid delivery before the invention was made, one of skill in the art would have known to replace one with the other, according to the needs.

The instant claims are drawn to (i) a deliverable composition comprising an amphipathic compound, polyvinylamine and siRNA (claim 1); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes and R1 and R3 are the same (claims 2 and 3), and (ii) a process for delivering a siRNA to an animal cell by using the above-mentioned composition, and wherein the animal cell is *in vivo*, *in vitro*, *ex vivo* or the cell is a mammalian cell (claims 5-9).

The patent claims recite a deliverable composition comprising an amphipatic compound, an ethoxylated polyethylenimine, and an siRNA (claim 1), wherein the amphipathic compound is a 1,4 disubstituted piperazine (claim 2), wherein the

substituting groups are C6 to C24 alkenes (claim 2), and wherein R1 and R2 are the same (claim 3). The patent claims do not recite polyvinylamine. Wolfert et al. teach that cationic polymers such as polyvinylamine efficiently condensate the nucleic acids and form small complexes with good extracellular stability (Abstract, p. 999, column 1, Results). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of the '995 patent by replacing the ethoxylated polyethylenimine with polyvinylamine and use it to deliver siRNAs to the nucleus, as taught by Wolfert et al., with a reasonable expectation of success. The motivation to do so is provided by Wolfert et al. who teach that the use of polyvinylamine results in small complexes that are stable in circulation, can undergo extravasation in the target tissues and can easily enter into the nucleus of target cells (Abstract, p. 1003, column 2, p. 1002, column 2) and by Leake et al., who teach the necessity of targeting the siRNAs to the nucleus to target non-coding nucleic acid sequences, such as promoters or enhancers (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). With respect to the limitations recited in the instant claims 6-8, they are not innovative over the prior art; one of skill in the art would have known that such compositions could be used to deliver siRNAs *ex vivo*, *in vivo*, or *in vitro*. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claims 1-3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application

No. 10/845,968. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a deliverable composition comprising an amphipathic compound, polyvinylamine and siRNA (claim 1); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes and R1 and R3 are the same (claims 2 and 3).

The patent claims recite a composition for the delivery of siRNA to mammalian cells, the composition comprising the siRNA, a first amphipatic compound, a second amphipathic compound, and a polycation that could be polyvinylamine (claim 1 and 2), wherein the first amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes (claim 3). It is noted that the patent claims do not require the first and second amphipathic compounds to be distinct and therefore, the claims read on an embodiment wherein the first and the second amphipathic compounds are the same. The specification discloses that R1 and R2 could be the same (see Fig. 3 for example). Thus, the application claims 1-3 anticipate the instant claims1-3. Since the US Application No. 10/845,968 claims 1-3 embrace all limitation of the instant claims, the instant claims and the application claim are obvious variants of one another.

Claim Rejections - 35 USC § 103

6. Claims 1-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al. (U.S. Patent No. 5,744,335, of record), in view of each Wolfert et al., Pollard et al. (J Biol Chem, 1998, 27: 7507-7511), and Leake et al., for the reasons of record set forth in the non-final Office action of 04/04/2006.

Applicant argues that the histone of Wolf et al. and the polyvinylamine (PVA) disclosed in the instant application cannot be considered to be structurally close and of common utility because (i) histones are naturally occurring protein with a three-dimensional structure designed to bind the genomic DNA, (ii) histones contain cationic, anionic, and hydrophobic groups, and (iii) polyvinylamine is a synthetic cationic polymer that does not have anionic or hydrophobic groups. For these reasons, Applicant argues that, while both molecule may be reasonable expected to ionically associate with all types of nucleic acid, they may not be reasonable anticipated to interact with both large plasmid DNA and oligonucleotides in a way that facilitates delivery to cells. Applicant submits that there is no evidence in the prior art to suggest that both a DNA-binding protein, such as a histone, and a synthetic polycation, such as polyvinylamine, would combine with an amphipatic compound to make an effective siRNA transfection agent. Applicant continues arguing that Wolfert et al. do not teach that polyvinylamine is a good nucleic acid delivery agent because they teach that (i) complexes between PVA and DNA tend to flocculate in water (Applicant concludes that flocculation of complexes can be expected to inhibit nucleic acid delivery), (ii) complexes between PVA and DNA gave no significant spontaneous transfection when applied to 293 cells *in vitro*, and (iii)

following direct inoculation into Xenopus oocytes, complexes between PVA and DNA showed over 60% expression as compared to other homopolymers (Applicant concludes that PVA inhibits transcription ability of the associated DNA, and therefore, Wolfert et al. teach that PVA inhibits DNA delivery). Additionally, Applicant submits that Wolfert et al. provide no teaching or suggestion on how any polymer will interact with oligonucleotides, such as siRNA or with amphipathic compounds for the delivery of the siRNA to a cell either *in vitro* or *in vivo*. Additionally, Applicant provides an attached Declaration under 37 CFR 1.132 showing that the replacement of histone with polyvinylamine in the teachings of Wolff et al. does not provide an effective DNA delivery agent, since delivery of DNA to 3T3 or CHO cells by PVA/lipid/DNA was not more effective than using DNA alone, whereas histone/lipid/DNA resulted in high levels of plasmid delivery.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

(i) The argument that histones and polyvinylamine cannot be reasonably anticipated to interact with both plasmids (i.e., large DNAs) and oligonucleotides (less than 30 base pairs) in a way that facilitates delivery to cells is just an argument not supported by the evidence of record. Arguments cannot take the place of evidence in the record. It is noted that Wolf et al. teach that their histone-containing composition can be used to deliver both plasmids and oligonucleotides to a mammalian cell (column 5, lines 46-60). Since the composition is suitable for oligonucleotide delivery, one of skill in the art would readily recognize that the composition of Wolff et al. (i.e., containing

histone) could also be used for similar short nucleotide sequences, such as siRNAs. There is no evidence in the art or in the specification that synthetic polymers, such as polyvinylamine, do not operate in the same way. On the contrary, the art teaches the suitability of synthetic polymers for the delivery of plasmids, oligonucleotides, and siRNAs to cells. Applicant's arguments are inconsistent with the instant specification which teaches against this argument, since it discloses that both natural proteins (such as histone) and synthetic polymers (such as polylysine and polyvinylamine) can be used to deliver siRNAs to the cells (p. 2, paragraphs 0010-0012). Therefore, it is clear that the art and other evidence of record does not support Applicant's argument.

(ii) The argument that there is no evidence in the prior art to suggest that both histones and synthetic polycations (i.e., polyvinylamine) can combine with an amphipatic compound to make an effective oligonucleotide transfection agent is again just an argument not supported by any evidence. The prior art teaches that practically any synthetic polycation and histones can be mixed with the claimed amphipatic compound (i.e., 1,4 disubstituted piperazine) to form an efficient siRNA transfection reagent (see for example the U.S. Patent No. 7,101,995 the inventors of which include the inventors of this application, column 4, lines 1-39).

(iii) Wolfert et al. do not need to provide teaching or suggestion on how polyvinylamine interacts with oligonucleotide such as siRNA or with amphipatic compounds. The rationale to modify the teachings of the prior art does not necessarily need to be expressly stated in the prior art. The rationale to modify can be implied from the prior art or from the knowledge available to one of skill in the art at the time the

invention was made (see MPEP 2144 [R5]). The following is a citation from MPEP 2144:

> THE EXPECTATION OF SOME ADVANTAGE IS THE STRONGEST RATIONALE FOR COMBINING REFERENCES
>
> The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

It is noted that Applicant misinterpreted the teachings of Wolfert et al. Wolfert et al. clearly teach that, after direct injection into Xenopus oocytes, complexes between DNA and all homopolymers tested (including PVA) showed levels of gene expression comparable to those following injection of free DNA, wherein the expression levels for all homopolymers was around 60%, with PVA and PAA over 60% and conclude that PVA and PAA form complexes that are efficient for nuclear transcription (see p. 996, Table 1, last column and p. 999, column 2, second full paragraph). Therefore, contrary to Applicant's argument, Wolfert et al. do not teach that PVA causes a reduction in transcription ability of the associated DNA, as compared to the other homopolymers. Moreover, Wolfert et al. teach that, although PVA-based complexes have low transfection activity, they efficiently condensate the nucleic acids and form small complexes suitable for systemic application and efficient for intranuclear transcription and suggest the design of particles with combined good extracellular stability and efficient intranuclear delivery/transcription, based on PVA (Abstract, p. 999, column 2, second full paragraph, p. 1002, column 2, p. 1003, column 2). Indirectly, through reference to Pollard et al., Wolfert et al. teach that it is the compaction of DNA (i.e., the

particle size) that improves nuclear targeting (see Pollard et al., p. 7511, column 1). It is noted that the prior art teaches the desirability to target siRNA to the cell nucleus. For example Wolff et al. teach nuclear targeting mediated by a nuclear localization signal linked to the histone (column 2, lines 15-27) and Leake et al. teach nuclear targeting to inhibit non-coding nucleic acid sequences, such as promoters or enhancers (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). Regarding Wolf et al., they teach that the addition of their amphipatic compound increases the transfection efficiency by several orders of magnitude (column 2, lines 7-14). Based on these teachings, one of skill in the art would have known that the small particles based on PVA would be better for nuclear targeting, as compared to the particles based on other polycations and would have been motivated to modify the method of Wolff et al. by replacing the histone with the polyvinylamine of Wolfert et al. to obtain monodisperse complexes of small size that combine good transfection activity with efficient nuclear targeting, characteristics taught by the prior art as main requirements for efficient gene delivery and expression (it is noted that in the case of siRNA, intranuclear delivery is enough for inhibiting target gene expression). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The Declaration under 37 CFR 1.132 filed on 12/11/2006 is insufficient to overcome the rejection of claims 1-3 and 5-9 based upon the references above as set forth in the last Office action because: the data presented do not pertain to the instant invention. The data presented in the Declaration describe the results obtained with a

complex between a lipid (it is not clear what lipid is used in the experiment), polyvinylamine, and DNA (not siRNA), whereas the instant invention is drawn to a complex between an amphipathic compound (wherein the amphipathic compound is 1,4 disubstituted piperazine, wherein the substituents are C6-C24 alkanes; this compound is not a lipid), polyvinylamine and siRNA. It is clear that these complexes are not identical and therefore it is not proper to extrapolate the data in the Declaration to the claimed complex. Moreover, it is noted that the complex in the declaration mediates the delivery of a DNA encoding a gene to be expressed, wherein expression requires transcription and translation, whereas the instant complex delivers siRNAs for inhibition og gene expression, wherein siRNAs only be present inside the cells for inhibition of gene expression (i.e., in the absence of transcription and translation). It is clear that these complexes are not structurally and functionally identical and therefore it is not proper to extrapolate the data in the Declaration to the claimed complex.

7. Claims 1-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being obvious over Lewis et al. (U.S. patent No. 7,101,995), in view of each Wofert et al., Pollard et al., and Leake et al.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an

invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Lewis et al. teach a deliverable composition comprising an amphipatic compound, an ethoxylated polyethylenimine (PEI), and an siRNA, wherein the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes, wherein R1 and R2 are the same (claims 1-3) and wherein the composition is used in a process of delivering siRNA to mammalian cells *in vivo* or *in vitro* (claims 5-7 and 9) (Abstract, column 4, lines 1-25, claims 1-3). Lewis et al. teach that siRNA could be targeted to the cytoplasm or nucleus, as needed (column 6, lines 14 and 15, column 7, lines 35-40). Lewis et al. do not teach polyvinylamine. Wolfert et al. teach that cationic polymers such as polyvinylamine efficiently condensate the nucleic acids and form small complexes with good extracellular stability (Abstract, p. 999, column 1, Results). Moreover, Wolfert et al. teach that, although PVA-based complexes have low transfection activity, they efficiently condensate the nucleic acids and form very small complexes suitable for systemic application and efficient for

intranuclear transcription and suggest the design of particles with combined good extracellular stability and efficient intranuclear delivery/transcription, based on PVA (Abstract, p. 999, column 2, second full paragraph, p. 1002, column 2, p. 1003, column 2). Indirectly, through reference to Pollard et al., Wolfert et al. teach that it is the compaction of DNA (i.e., the particle size) that improves nuclear targeting (see Pollard et al., p. 7511, column 1). Based on these teachings, one of skill in the art would have known, at the time the invention was made that the small particles based on PVA would be better for nuclear targeting, as compared to the particles based on other polycations and would have been motivated to modify the method of Lewis et al. by replacing the ethoxylated PEI with the polyvinylamine of Wolfert et al. to obtain monodisperse complexes of small size that combine good transfection activity with efficient nuclear targeting, characteristics taught by the prior art as main requirements for efficient gene delivery and expression (see Wolfert et al., p. 1002, column 2, p. 1003, column 2). One of skill in the art would have been motivated to target an siRNA to the nucleus to inhibit the activity of non-coding nucleic acid sequences, such as promoters and enhancers, as taught by Leake et al. (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such compositions can be successfully made and used. With respect to the limitation recited in the instant claim 8, this is not innovative over the prior art; one of skill in the art would have known that such

compositions could also be used to deliver siRNAs *ex vivo*. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. It is noted that Applicant's argument were sufficient to obviate the rejection of claims 1-3 and 5-9 under 35 U.S.C. 103(a) as being unpatentable over Wolff et al., in view of Meier et al. (U.S. Patent No. 6,616,946). The rejection was made in the final Office action of 09/19/2006.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Jon Weber
AU 1633